REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

By the foregoing amendment, claims 21 and 33 have been amended to further clarify Applicant's invention. Support for the amendments can be found throughout the specification. Specifically, support can be found in the specification on page 13, last paragraph. Accordingly no new matter has been added.

I. Rejections under 35 U.S.C. § 112, second paragraph

Claims 21-29 and 41-43 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

Specifically, claims 21 and 33 have been rejected for reciting the phrase "same reaction zone" because the Examiner is not clear whether applicants are claiming common sequences on a plurality of DNA templates where hybridization reactions takes place or whether applicants are claiming the zone of immobilization reaction by which the single stranded nucleotides are attached on one end to the solid support. Applicants respectfully traverse this rejection.

Applicants submit that the "reaction zone" is a region of a solid support where the single-stranded templates are immobilized. A key difference between the present invention

and the prior art is that with the present invention more than one single-stranded DNA is present in the target DNA population, in a unique amount and in the same reaction zone. However, in order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, applicants have amended claims 21 and 33 to recite "a heterogeneous population of single-stranded DNAs to be sequenced, each of which is immobilized in a unique amount in the same reaction zone . . . ." This amendment to claims 21 and 33 clarifies that the single-stranded DNA population is heterogeneous and need not have a particular common sequence. Further, the amendment clarifies that the reaction zone is the location where the single-stranded DNAs are immobilized. This amendment, however, is not intended to limit the scope of the claims or any element recited therein.

In view of the above, applicants respectfully request withdrawal of the rejection of claims 21 and 33 under 35 U.S.C. § 112, second paragraph.

II. Rejections under 35 U.S.C. § 102(b)

Claims 21-32 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Southern et al. (WO 95/04160). Applicants respectfully traverse this rejection.

It is well settled law that to anticipate a claim, a single reference must teach each and every element of the claim, and the single reference must be enabling. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir.

1986); *Atlas Powder Co. v. E.I du Pont De Nemours & Co.*, 750 F.2d 1569, 1574, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984).

Applicants submit that the presently-claimed invention is directed to a method for sequencing multiple DNA templates in the same reaction zone. By contrast, the method disclosed in Southern et al., in particular pages 14 to 21 of Southern et al., is suitable only for sequencing a single DNA template. While Southern et al. does disclose the sequencing of multiple templates in parallel, each of these templates, however, are present in its own distinct reaction zone (*e.g.*, on a pin) and sequencing involves simply carrying out the disclosed method of each template separately.

The type of parallel analysis of multiple templates as described in Southern et al. represents a fundamentally different problem from the analysis of multiple templates in the same reaction zone as set forth in the present invention. In particular, if multiple templates are to be analyzed in a single reaction zone, there must be some method of analyzing the data from the reaction zone so that particular data can be assigned to the particular template that generated it.

For this reason, the presently-claimed invention requires that each DNA template is present in the reaction zone in a unique amount. In any given sequencing cycle, the frequency of (or signal size from) each probe will vary with the amount of the complementary DNA template present in the reaction zone.

By comparison, Southern et al. is not concerned with the problem of analyzing multiple templates in the same reaction zone, and thus, the method of Southern et al. would not be suitable for that purpose.

Applicants note that the Examiner's rejection is based on the assumption that "same reaction zone" means a common sequence on a plurality of DNA templates where the hybridization reaction takes place. However, applicants have amended claim 21 to indicate that the single-stranded DNA population is heterogeneous and need not have a particular common sequence. Further, the amendment to claim 21 indicates that the reaction zone is the location where the single-stranded DNAs are immobilized. Southern et al. does not teach or suggest this feature of the present invention.

Because Southern et al. does not teach each and every element of the claimed invention, as required by law, the reference can not anticipate the claimed invention. Therefore, applicants respectfully request withdrawal of the rejection of claims 21-32 under 35 U.S.C. § 102(b).

Claims 21-25 and 27-32 have been rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Macevicz et al. (WO 96/33205). Applicants respectfully traverse this rejection.

Applicants submit that the presently-claimed invention is distinct from the disclosure in Macevicz et al., on the basis that Macevicz et al. does not disclose a method for sequencing multiple different templates in the same reaction zone.

Macevicz et al. instead provides a method for analyzing a single nucleic acid template by dividing a population comprising multiple copies of that template into several reaction zones. In each reaction zone, a different initializing oligonucleotide is added to the target template so that each initializing oligonucleotide starts sequencing at a different point in the target sequence. For example, each oligonucleotide may start the sequencing reaction one base further along the target. Probe oligonucleotides are then ligated to the initializing oligonucleotide, identifying the base adjacent to the initializing oligonucleotide. In this way, several bases of the sequence are identified for each target, but at the expense of having multiple parallel reaction zones for each template.

The method of Macevicz et al. is therefore entirely different from the presently-claimed method in which multiple different templates are sequenced simultaneously in the same reaction zone.

It appears that the Examiner has not made a distinction between (a) a target population which comprises more than one copy of the single nucleic acid template in a single reaction zone; and (b) a target population in which there are several different nucleic acid templates, each template being present in multiple copies in the reaction zone, and each template being present in a unique amount with respect to the other templates in the reaction zone.

Furthermore, it would not be possible for the skilled artisan to arrive at the presently-claimed method by combining the teaching of Southern et al. and Macevicz et al.

since Macevicz et al. also does not address the problem of sequencing multiple different templates in one reaction zone.

Southern et al. and Macevicz et al. are concerned only with the type (a) target population while the presently-claimed method is concerned with the type (b) target population. However, in order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, applicants have amended claim 21 to indicate that the single-stranded DNA population is heterogeneous and need not have a particular common sequence. Further, the amendment to claim 21 clarifies that the reaction zone is the location where the single-stranded DNAs are immobilized.

Because Macevicz et al. does not teach each and every element of the claim, as required by law, the reference can not anticipate the claimed invention. Therefore, applicants respectfully request withdrawal of the rejection of claims 21-25 and 27-32 under 35 U.S.C. § 102(a).

III. Rejections under 35 U.S.C. § 103(a)

Claims 21-39 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Southern et al. (WO 95/04160) in view of Stratagene Catalog (1988, page 39). Specifically, the Examiner has stated that Southern et al. teaches the method of claims 1-12 including an array of hybridization probes comprising mass labels and the Stratagene catalog teaches a motivation to combine reagents into kit format. Based thereon, the Examiner has concluded that it would have been obvious to one of ordinary skill in the

art to combine all the reagents into a kit format. Applicants respectfully traverse this rejection.

Applicants submit that, as noted above, Southern et al. does not address the problem of sequencing multiple different templates in the same reaction zone. The method disclosed in Southern et al. would not be suitable for this purpose, and there is no teaching or suggestion in the document of how the method might be adapted to make it suitable. Indeed, Southern et al. is silent with regard to sequencing different multiple templates in one reaction zone. Upon reading Southern et al. the skilled artisan would not be motivated to attempt to adapt the teaching of Southern et al. to arrive at a method falling within the scope of present invention.

As discussed above, the presently-claimed invention provides a method for sequencing multiple different templates in the same reaction zone. The method requires that each template is present in the reaction zone in a unique amount. In any given sequencing cycle, a probe can be linked with a particular template or templates on the basis that the signal size from each probe will vary with the amount of the complementary DNA template present in the reaction zone.

Claims 21 and 33 of the present application indicate that the single-stranded DNA population is heterogeneous and need not have a particular common sequence. Further, claims 21 and 33 indicate that the reaction zone is the location where the single-stranded DNAs are immobilized.

Neither Southern et al. nor the Stratagene Catalog, singly or in combination, disclose the invention as claimed. In particular, neither document discloses a means for resolving hybridization data obtained from a heterogenous population of DNA templates from the same reaction zone, based on the unique amount in which each of the templates is present in the reaction zone.

It would not be possible for a skilled person to combine the teaching of Southern et al. with the contents of the cited Stratagene Catalog in order to arrive at the present invention.

Therefore, applicants respectfully request withdrawal of the rejection of claims 21-39 under 35 U.S.C. § 103(a).

IV. Objections under 35 U.S.C. § 132

The Examiner has objected to the amendment filed on October 12, 2000 because it allegedly introduces new matter in the disclosure of claims 33, 36, 41-43. The Examiner has stated that there is no support for a "kit with plurality of DNA templates each present in unique amount in the same reaction zone with a means for resolving a measured quantity of hybridized probe by computer program with an algorithm." The Examiner has requested that the new matter be canceled in a reply to the Official Action. Applicants respectfully traverse this objection.

Applicants submit that the specification provides support for the amendment. Specifically, the specification, on page 5, lines 18-19, states that "[u]se of the kit is therefore

provided for a method of sequencing DNA, especially the method described above." Therefore, the kit of the invention is used to perform the method of the invention, which encompasses the language recited in amended claim 33 and new claims 42-43 (*i.e.*, a kit with a heterogeneous population of DNA templates each present in a unique amount in the same reaction zone with a means for resolving a measured quantity of hybridized probe by computer program with an algorithm). Further, applicants remind the Examiner that support for this language can be found on pages 14-15 and throughout the specification.

Accordingly, the Examiner is respectfully requested to withdraw the new matter objection.

From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order and such action is earnestly solicited.

In the event that there are any questions relating to this Amendment and Reply, or the application in general, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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Attachment to Amendment dated April 9, 2001
Marked-up Claims

21. (Amended) A method for sequencing DNA, which comprises:

(a) obtaining a target DNA population comprising a [plurality] heterogeneous population of single-stranded DNAs to be sequenced, each of which is [present] immobilized in a unique amount in the same reaction zone and bears a primer to provide a double-stranded portion of the DNA for ligation thereto;

(b) contacting the DNA population with an array of hybridization probes, each probe comprising a label cleavably attached to a known base sequence of predetermined length, the array containing all possible base sequences of that predetermined length and the base sequences being incapable of ligation to each other, wherein the contacting is carried out in the presence of ligase under conditions to ligate to the double-stranded portion of each DNA the probe bearing the base sequence complementary to the single-stranded DNA adjacent the double-stranded portion thereby to form an extended double stranded portion which is incapable of ligation to further probes; and

(c) removing all unligated probes; followed by the steps of:

(d) cleaving the ligated probes to release each label;

(e) recording the quantity of each label; and

(f) activating the extended double-stranded portion to enable ligation thereto;

wherein

(g) steps (b) to (f) are repeated in a cycle for a sufficient number of times to determine the sequence of each single-stranded DNA by determining the sequence of release of each label.

33. (Twice Amended) A kit for sequencing a [plurality] heterogeneous population of DNA templates, each [present] immobilized in a unique amount in the same reaction zone, which kit comprises:

(a) an array of hybridization probes, each probe comprising a label cleavably attached to a known base sequence of predetermined length, the array containing all possible base sequences of that predetermined length and the base sequences being incapable of ligating to each other; and

(b) a means for resolving a measured quantity of a hybridized probe into quantities which correspond to unique amounts of the templates to which the probe hybridizes.